

CHLORAMPHENICOL SODIUM SUCCINATE - chloramphenicol sodium succinate injection, powder, lyophilized, for solution
Fresenius Kabi USA, LLC

CHLORAMPHENICOL SODIUM SUCCINATE

FOR INJECTION, USP

FOR INTRAVENOUS ADMINISTRATION

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the INDICATIONS section. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.*

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

IMPORTANT CONSIDERATIONS IN PRESCRIBING CHLORAMPHENICOL SODIUM SUCCINATE FOR INJECTION:

Chloramphenicol sodium succinate for injection is intended for IV use only. It has been demonstrated to be ineffective when given intramuscularly.

- Chloramphenicol sodium succinate for injection must be hydrolyzed to its microbiologically active form and there is a big lag in achieving adequate blood levels compared with the base given IV.
- The oral form of chloramphenicol is readily absorbed and adequate blood levels are achieved and maintained on the recommended dosage.
- Patients started on IV chloramphenicol sodium succinate for injection should be changed to the oral form as soon as practicable.

DESCRIPTION:

Chloramphenicol is an antibiotic that is clinically useful for, and *should be reserved for*, serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. Sensitivity testing is essential to determine its indicated use, but may be performed concurrently with therapy initiated on clinical impression that one of the indicated conditions exists (see **INDICATIONS** section).

Each gram (10 mL of a 10% solution) of chloramphenicol sodium succinate for injection contains approximately 52 mg (2.25 mEq) of sodium.

CLINICAL PHARMACOLOGY:

In vitro chloramphenicol exerts mainly a bacteriostatic effect on a wide range of gram-negative and gram-positive bacteria and is active *in vitro* against rickettsias, the lymphogranuloma-psittacosis group and *Vibrio cholerae*. It is particularly active against *Salmonella typhi* and *Hemophilus influenzae*. The mode of action is through interference or inhibition of protein synthesis in intact cells and in cell-free systems.

Chloramphenicol administered orally is absorbed rapidly from the intestinal tract. In controlled studies in adult volunteers using the recommended dosage of 50 mg/kg/day, a dosage of 1 g every 6 hours for 8 doses was given. Using the microbiological assay method, the average peak serum level was 11.2 mcg/mL one hour after the first dose. A cumulative effect gave a peak rise to 18.4 mcg/mL after the fifth dose of 1 g. Mean serum levels ranged from 8 to 14 mcg/mL over the 48-hour period. Total urinary excretion of chloramphenicol in these studies ranged from a low of 68% to a high of 99% over a three-day period. From 8 to 12% of the antibiotic excreted is in the form of free chloramphenicol; the remainder consists of microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most chloramphenicol detected in the blood is in the microbiologically active free form. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol is relatively high, amounting to several hundred mcg/mL in patients receiving divided doses of 50 mg/kg/day. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half of those found in blood. Measurable levels are also detected in pleural and in ascitic fluids, saliva, milk and in the aqueous and vitreous humors. Transport across the placental barrier occurs with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

INDICATIONS:

In accord with the concepts in the WARNING box and this INDICATIONS section, chloramphenicol must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions below is believed to be present; *in vitro* sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests. The decision to continue use of chloramphenicol rather than another antibiotic when both are suggested by *in vitro* studies to be effective against a specific pathogen should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, efficacy of the various drugs in the infection and the important additional concepts contained in the WARNING box above.

- **Acute infections caused by *Salmonella typhi****

It is not recommended for the routine treatment of the typhoid carrier state.

- **Serious infections caused by susceptible strains in accordance with the concepts expressed above:**

- a) *Salmonella* species
- b) *H. influenzae*, specifically meningeal infections
- c) Rickettsia
- d) Lymphogranuloma-psittacosis group
- e) Various gram-negative bacteria causing bacteremia, meningitis or other gram-negative infections.
- f) Other susceptible organisms which have been demonstrated to be resistant to all other appropriate

antimicrobial agents.

- **Cystic fibrosis regimens**

*In the treatment of typhoid fever some authorities recommended that chloramphenicol be administered at therapeutic levels for 8 to 10 days after the patient has become afebrile to lessen the possibility of relapse.

CONTRAINDICATIONS:

Chloramphenicol is contraindicated in individuals with a history of previous hypersensitivity and/or toxic reaction to it. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infection.*

PRECAUTIONS:

Baseline blood studies should be followed by periodic blood studies approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia or any other blood study findings attributable to chloramphenicol. However, it should be noted that such studies do not exclude the possible later appearance of the irreversible type of bone marrow depression.

Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk or relapse of the disease.

Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.

Excessive blood levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the blood concentration should be determined at appropriate intervals.

There are no studies to establish the safety of this drug in pregnancy.

Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (gray syndrome).

Precaution should be used in therapy of premature and full-term infants to avoid “gray syndrome” toxicity (see **ADVERSE REACTIONS**). Serum drug levels should be carefully followed during therapy of the newborn infant.

Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.

The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

ADVERSE REACTIONS:

Blood Dyscrasias

The most serious adverse effect of chloramphenicol is bone marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia and granulocytopenia) are

known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance weeks or months after therapy of bone marrow aplasia or hypoplasia. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed.

A reversible type of bone marrow depression, which is dose related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes and leukopenia, and responds promptly to the withdrawal of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding 1) the size of the population at risk, 2) the total number of drug-associated dyscrasias, 3) the total number of non-drug associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia.

Paroxysmal nocturnal hemoglobinuria has also been reported.

Gastrointestinal Reactions

Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

Neurotoxic Reactions

Headache, mild depression, mental confusion and delirium have been described in patients receiving chloramphenicol; optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

Hypersensitivity Reactions

Fever, macular and vesicular rashes, angio-edema, urticaria and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

"Gray Syndrome"

Toxic reactions including fatalities have occurred in the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the gray syndrome. One case of gray syndrome has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month old infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

- a) In most cases therapy with chloramphenicol had been instituted within the first 48 hours of life.
- b) Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol.
- c) The symptoms appeared in the following order:
 - 1) abdominal distension with or without emesis;

2) progressive pallid cyanosis;

3) vasomotor collapse, frequently accompanied by irregular respiration;

4) death within a few hours of onset of these symptoms.

d) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.

e) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg/mL after repeated doses).

f) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

ADMINISTRATION:

Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Administration of 50 mg/kg/day in divided doses will produce blood levels of the magnitude to which the majority of susceptible microorganisms will respond.

As soon as feasible an oral dosage form of chloramphenicol should be substituted for the IV form because adequate blood levels are achieved with chloramphenicol by mouth.

The following method of administration is recommended:

Intravenously as a 10% (100 mg/mL) solution to be injected over at least a one-minute interval. This is prepared by the addition of 10 mL of an aqueous diluent such as Water for Injection or 5% Dextrose Injection.

DOSAGE:

Adults

Adults should receive 50 mg/kg/day in divided doses at 6-hour intervals. In exceptional cases patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible. Adults with impairment of hepatic or renal function or both may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under ***Newborn Infants.***) Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques.

Children

Dosage of 50 mg/kg/day divided into 4 doses at 6-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (e.g. bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible. Children with impaired liver or kidney function may retain excessive amounts of the drug.

Newborn Infants

(See section titled “Gray Syndrome” under ADVERSE REACTIONS.) A total of 25 mg/kg/ day in 4 equal doses at 6-hour intervals usually produces and maintains concentrations in blood and tissues adequate to control most infections for which the drug is indicated. Increased dosage in these

individuals, demanded by severe infections, should be given only to maintain the blood concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg/kg/ day equally divided into 4 doses at 6-hour intervals. *These dosage recommendations are extremely important because blood concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants.* This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.

Infants and Children with Immature Metabolic Processes

In young infants and other children in whom immature metabolic functions are suspected, a dose of 25 mg/kg/day will usually produce therapeutic concentrations of the drug in the blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques.

HOW SUPPLIED:

Chloramphenicol Sodium Succinate for Injection, USP is freeze-dried in the vial. When reconstituted as directed, each vial contains a sterile solution equivalent to 100 mg of chloramphenicol per mL (1 g/10 mL).

Product No.	NDC No.	
1115	63323-011-15	Available in packages of 10 vials.

Preservative Free.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].



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Revised: April 2015

PACKAGE LABEL - PRINCIPAL DISPLAY - Chloramphenicol Sodium Succinate 1 gram Vial Label

NDC 63323-011-15

1115

Chloramphenicol Sodium Succinate For Injection, USP

equivalent to **1 gram** Chloramphenicol

Rx only

For Intravenous Use Only

NDC 63323-011-15 1115

CHLORAMPHENICOL SODIUM SUCCINATE
FOR INJECTION, USP
equivalent to

1gram

Chloramphenicol
Rx only
For Intravenous Use Only

Sterile, Lyophilized
Preservative Free
Usual Adult Daily Dosage: 50 mg per kg.
See insert. Contents have been
lyophilized in vial.

To prepare a 10% (100 mg/mL) solution,
add 10 mL of sterile aqueous diluent
such as Sterile Water for Injection or 5%
Dextrose Injection. When reconstituted
as directed, 10 mL contains the
equivalent of 1 gram chloramphenicol.

WARNING: Blood dyscrasias may be
associated with the use of chloram-
phenicol. It is essential that adequate
blood studies be made. See enclosed
WARNINGS and PRECAUTIONS.

A cloudy solution should not be used.
Keep this and all drugs out of the reach
of children.

Store at 20° to 25°C (68° to 77°F) [see
USP Controlled Room Temperature].

FRESINIUS KABI
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Lake Zurich, IL 60047

401863G
LOT/EXP



CHLORAMPHENICOL SODIUM SUCCINATE

chloramphenicol sodium succinate injection, powder, lyophilized, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:63323-011
Route of Administration	INTRAVENOUS	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CHLORAMPHENICOL SODIUM SUCCINATE (UNII: 872109HX6B) (CHLORAMPHENICOL - UNII:66974FR9Q1)	CHLORAMPHENICOL	1 g in 10 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63323-011-15	10 in 1 TRAY		
1		10 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA062365	01/12/2001	

Labeler - Fresenius Kabi USA, LLC (608775388)

Establishment

Name	Address	ID/FEI	Business Operations
Fresenius Kabi USA, LLC		023648251	MANUFACTURE(63323-011)